NUCLEIC ACID SEQUENCING PROCESSES USING NON-RADIOACTIVE DETECTABLE MODIFIED OR LABELED NUCLEOTIDES OR NUCLEOTIDE ANALOGS, AND OTHER PROCESSES FOR NUCLEIC ACID DETECTION AND CHROMOSOMAL CHARACTERIZATION USING SUCH NON-RADIOACTIVE DETECTABLE MODIFIED OR LABELED NUCLEOTIDES OR NUCLEOTIDE ANALOGS

REFERENCE TO OTHER RELATED APPLICATIONS

This application is a continuation of U.S. patent application Ser. No. 07/954,772, filed on Sep. 30, 1992, which application was abandoned in favor of the present application. Ser. No. 07/954,772 was a continuation of U.S. patent application Ser. No. 07/548,348, filed on Jul. 2, 1990 (abandoned), which was a divisional application of U.S. patent application Ser. No. 07/140,980, filed on Jan. 5, 1988 (abandoned), which was a continuation of U.S. patent application Ser. No. 06/674,352, filed on Nov. 21, 1984 (abandoned), the latter being a continuation of U.S. patent application Ser. No. 06/391,440, filed on Jun. 23, 1982 (abandoned). Two other applications were filed as divisional applications of the aforementioned Ser. No. 07/140,980: U.S. patent application Ser. No. 07/532,704, filed on Jun. 4, 1990; and U.S. patent application Ser. No. 07/567,039, filed on Aug. 13, 1990. Ser. No. 07/532,704 issued on Aug. 31, 1993 as Engelhardt et al., U.S. Pat. No. 5,241,060, and is titled "Base Moiety-Labeled Detectable Nucleotide." Ser. No. 07/567,039 issued on Nov. 9, 1993 as Engelhardt et al., U.S. Pat. No. 5,260,433, and is titled "Saccharide Specific Binding System Labeled Nucleotides.

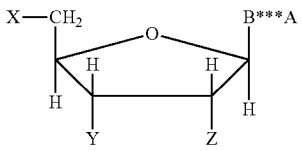
BACKGROUND OF THE INVENTION

It is known to produce nucleotides or polynucleotides which are radioactively labeled, such as with isotopes or hydrogen (^3H), phosphorus (^{32}P), carbon (^{14}C) or iodine (^{125}I). Such radioactively labeled compounds are useful to detect, monitor, localize and isolate nucleic acids and other molecules of scientific or clinical interest. Unfortunately, however, the use of radio-actively labeled materials presents hazards due to radiation. Also due to the relatively short half life of the radioactive materials employed to label such compounds or materials, the resulting labeled compounds or materials have a corresponding relatively short shelf life.

It has been proposed to chemically label compounds of interest, such as nucleotides and polynucleotides, so as to overcome or avoid the hazards and difficulties associated with such compounds or materials when radioactively labeled. In the article by P. R. Langer, A. A. Waldrop and D. C. Ward entitled "Enzymatic Synthesis of Biotin-Labeled Polynucleotides: Novel Nucleic Acid Affinity Probes", in *Proc. Natl. Acad. Sci., USA, Vol.* 78, No. 11, pp. 6633-6637, November, 1981, there are described analogs of dUTP and UTP that contain a biotin molecule bound to the C-5 position of the pyrimidine ring through an alkylamine linker arm. The biotin-labeled nucleotides are efficient substrates for a variety of DNA and RNA polymerases in vitro. Polynucleotides containing low levels of biotin substitution (50 molecules or fewer per kilobase) have denaturation, reassociation and hybridization characteristics similar to those of unsubstituted controls. Biotin-labeled polynucleotides, both single and double stranded, are selectively and quantitatively retained on avidin-Sepharose, even after extensive washing with 8M urea, 6M guanidine hydrochloride or 99% formamide. In addition, biotin-labeled nucleotides can be selectively immunoprecipitated in the presence of antibiotin antibody and *Staphylococcus aurea*, Protein A. These unique features of biotin-labeled polynucleotides suggest that they are useful affinity probes for the detection and isolation of specific DNA and RNA sequences. It is indicated in the article that the subject matter of the article is comprised in a pending U.S. patent application.

The disclosures of this article and above-referred pending patent application are herein, incorporated and made part of this disclosure.

The patent application referred to in the above-identified article is U.S. patent application Ser. No. 255,223 filed Apr. 17, 1981. Ser. No. 06/255,223 was abandoned in favor of continuation application, U.S. patent application Ser. No. 06/496,915, filed on May 23, 1983, now U.S. Pat. No. 4,711,955. A related divisional application of the aforementioned Ser. No. 06/496,915 was filed as U.S. patent application Ser. No. 07/130,070 (on Dec. 8, 1987), and has since issued on Jul. 12, 1994 as U.S. Pat. No. 5,328,824. Two related continuation applications of the aforementioned Ser. No. 07/130,070 were filed on Feb. 26, 1992 (as Ser. No. 07/841,910) and on May 20, 1992 as (Ser. No. 07/886,660). In the above-identified pending U.S. patent application the subject matter of the above-identified article is disclosed and additionally it is disclosed that compounds having the structure:



wherein B represents a purine, deazapurine, or pyrimidine moiety covalently bonded to the C^1-position of the sugar moiety, provided that when B is purine or 7-deazapurine, it is attached at the N^9-position of the purine or deazapurine, and when B is pyrimidine, it is attached at the N^1-position;

wherein A represents a moiety consisting of at least three carbon atoms which is capable of forming a detectable complex with a polypeptide when the compound is incorporated into a double-stranded ribonucleic acid, deoxyribonucleic acid duplex, or DNA-RNA hybrid;

wherein the dotted line represents a chemical linkage joining B and A, provided that if B is purine the linkage is attached to the 8-position of the purine, if B is 7-deaza-purine, the linkage is attached to the 7-position of the deazapurine, and if B is pyrimidine, the linkage is attached to the 5-position of the pyrimidine; and

wherein each of x, y, and z represents